보건학석사 학위논문

Exposure Assessment of Three Antineoplastic Drugs During Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Surgery

고압복강항암화학요법 시술 시 세 가지 항암제에 대한 노출 평가

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지도교수 윤 충 식

이 논문을 보건학석사 학위논문으로 제출함

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Abstract

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Objective To improve the quality of life for patients with poor prognosis due to the difficulty of treating peritoneal carcinomatosis, pressurized intraperitoneal aerosol chemotherapy (PIPAC) has recently been developed in Europe. However, this method could expose healthcare workers to antineoplastic drugs, and limited research into such exposure has been conducted. The purpose of

this study was to evaluate the potential for occupational exposure to antineoplastic drugs during the process of PIPAC surgery in Korea.

Methods The PIPAC procedure using antineoplastic drugs was conducted in the operating room. The procedure was applied to swine using three antineoplastic drugs including paclitaxel, cisplatin, and doxorubicin. Surface samples were collected from directly exposed devices and protective equipment. Air samples were collected near the operating table at the locations of healthcare workers during the procedure. Paclitaxel and doxorubicin were analyzed using ultra-high-performance liquid chromatography (HPLC). Cisplatin was analyzed with inductively coupled plasma mass spectrometry (ICP-MS).

Results Of the total 101 wipe samples and 56 air samples, 81 (80.2%) and 9 (16.1%) were contaminated, respectively. Among wipe samples, 86.5% (45 of 52) of samples from PIPAC devices were contaminated. The geometric mean (GM) of paclitaxel and platinum were 1.94 ng/cm^2 (GSD, 5.12; range 0.39–76.75 ng/cm^2) and 2.14 ng/cm^2 (GSD, 7.73; range 0.02–235.1 ng/cm^2), and the concentration ranges of the drugs were 0.39–76.75 ng/cm^2 and 0.02–235.09 ng/cm^2, respectively. Doxorubicin was detected in 3 of 10 samples, ranging from below the limit of detection (LOD) to 3.86 ng/cm^2. The contaminated samples of personal protective equipment accounted for 80% (36 of 45). Testing for paclitaxel and platinum on the surgeon's and nurse's protective equipment found paclitaxel concentrations ranging from below the LOD to 0.62 ng/cm^2, and platinum was from below the LOD to 0.23 ng/cm^2; four samples of doxorubicin were below the LOD. In air samples, paclitaxel was detected (9

of 12) at up to 87.81 ng/m^3 from below the LOD (GM, 37.38 ng/m^3). Neither platinum (n = 16) nor doxorubicin (n = 28) was detected in air.

Conclusions In the process of developing and introducing PIPAC as a novel chemotherapy method in Korea, occupational exposure to three antineoplastic drugs was evaluated. Since more than 80% of wipe samples of three antineoplastic drugs during PIPAC surgery, care should be taken to minimize dermal exposure. The surface might be contaminated due to leaks of the antineoplastic drug in the process of preparing, diluting, injecting, handling and disposing of the drugs. The possibility of inhalation exposure to two drugs (doxorubicin, cisplatin) was low, because they were not observed in the air, while paclitaxel was detected low in the air. Even though there were no exposure limits for these antineoplastic drugs, it should be kept as low as possible.

Keywords: Pressurized intraperitoneal aerosol chemotherapy, PIPAC, chemotherapy, antineoplastic drug, occupational exposure, healthcare worker

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1. Introduction

Peritoneal carcinomatosis (PC) poses a therapeutic challenge due to the difficulty of treatment and poor prognosis. It has generally been treated with systemic chemotherapy, generally administered as an intravenous injection. To increase the average life expectancy and improve the quality of life, PC is currently treated using multimodal therapy combining cytoreductive surgery (CRS), which eliminates cancer tissues in the peritoneum, with hyperthermic intraperitoneal chemotherapy (HIPEC) to remove residual cancer cells through direct injection of liquid antineoplastic drugs (Facchiano et al., 2008; Verwaal et al., 2008).

The technique of spraying antineoplastic drugs as aerosols was introduced due to its greater feasibility, safety, and efficacy compared to treatment combining CRS and HIPEC (Reymond et al., 2000). Antineoplastic drugs in aerosol form have been shown to increase the depth of drug penetration into tissues, extend drugs' surface distribution, and improve patient outcomes compared to CRS and HIPEC, with many side effects reduced. A new technique referred to as pressurized intraperitoneal aerosol chemotherapy (PIPAC) was introduced in 2012 (Solaß et al., 2012). The general PIPAC process comprises several steps, including insufflating carbon dioxide (CO_2) into the peritoneum to inflate it and then spraying antineoplastic drugs from a syringe into the peritoneum under high pressure (Khosrawipour et al., 2016).

The antineoplastic drugs used in pre-clinical and clinical studies of PIPAC are

similar to those used in systematic chemotherapy and HIPEC, including doxorubicin, paclitaxel, and platinum compounds (e.g. cisplatin, oxaliplatin). Frequently used drugs in PIPAC, such as doxorubicin and cisplatin, have been classified as likely carcinogenic substances to humans (Group 2A) by the International Agency for Research on Cancer (IARC monograph, 1987). Paclitaxel has been classified as having positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans (Pregnancy Category D) by the Food and Drug Administration (FDA) (WHO, 2013). Hence, antineoplastic drugs used in PIPAC could have serious health effects such as carcinogenicity, teratogenicity, reproductive toxicity, and other organ toxicity at low doses (NIOSH, 2004; NIOSH, 2012).

The issue of occupational exposure in the PIPAC procedure has been raised, and several reports have used exposure assessments rather than clinical studies. Previous research into occupational exposure during PIPAC has provided evaluations of surface and air contamination levels. The greatest potential risk was dermal exposure during the process of handling, injecting, and disposing of the antineoplastic drugs used for PIPAC treatment (Reymond, 2015). The surface contamination levels associated with PIPAC have also been investigated. The syringe holder used for PIPAC measured in the range of 0.005–0.3 ng/cm^2, and the gloves of the surgeon had a median of 0.004 ng/cm^2 (Willaert et al., 2017; Ametsbichler et al., 2018). However, it was difficult to determine the levels of contamination on directly exposed devices. Paclitaxel was not evaluated for occupational exposure through PIPAC. Furthermore, the particle

size of aerosols sprayed from the nozzle was about 3–15 μm, creating a potential inhalation risk due to injection trocar leakage (Khosrawipour et al., 2016). A study that measured platinum for the analysis of platinum compound drugs (e.g. cisplatin, oxalipatin) reported that it was below the limit of detection (LOD) in the air during PIPAC (Solaß et al., 2013; Graversen et al., 2016).

Although aerosolization of antineoplastic drugs is known to increase their depth of penetration into cells, no studies of PIPAC using precessional motion to improve efficiency have been reported (Khosrawipour et al., 2016). Precessional motion in PIPAC might increase the risk of aerosols leaking from the abdominal cavity. Therefore, it is essential to assess exposure of healthcare workers during the technological development stage by adding precessional motion to the PIPAC procedure. In addition, an exposure assessment study using paclitaxel is yet to be conducted.

The first PIPAC procedure was reported in Europe in 2012. In Korea, the procedure has been used with precessional motion since 2018. This study was conducted in a swine model with the same protocol and conditions as applied in humans, as it was necessary to evaluate potential occupational exposure to antineoplastic drugs during this procedure.

This study aimed to evaluate inhalation and dermal exposure to three antineoplastic drugs via surface and air contamination during the PIPAC procedure with precessional motion.

2. Materials and methods

2.1. Selection of antineoplastic drugs and PIPAC procedures

Three types of antineoplastic drugs were used in the PIPAC procedures: paclitaxel (40 mg in 80 ml NaCl 0.9%), cisplatin (14.7 mg in 70 ml NaCl 0.9%), and doxorubicin (3.5 mg in 50 ml NaCl 0.9%). For each of these drugs, 50 ml was injected into the PIPAC syringe for spraying.

The PIPAC procedure was performed using a total of 18 experimental swine (paclitaxel, 5 swine; cisplatin, 6 swine; doxorubicin, 7 swine) between June and December 2018. The procedures with paclitaxel and cisplatin both employed precessional motion. In three instances of the procedure using doxorubicin (trial no. 8, one swine; no. 10, the second of three swine; no. 11, the second of two swine), precessional motion was not applied to evaluate its applicability.

The PIPAC procedure involved insertion of two 5 mm trocars (Nos. 1, 2) (Model: transport-TR12F, Dalimsurg NET Inc., Republic of Korea) into the abdominal cavity to ensure tightness. CO_2 insufflation was then conducted using one trocar (No. 2) to maintain a constant pressure of 1,600 Pa in the abdominal cavity. Then, 50 ml of each prepared drug was injected into the syringe. Next, the drug was transferred from the syringe to a spraying nozzle (nebulizer) made of stainless steel through a connecting tube. The spraying nozzle was inserted into the second trocar (No. 1) for spraying (flow rate 30 ml/min). At this time, a telescope was inserted into the trocar (No. 2) with the CO_2 hose to observe the inside of the abdominal cavity. After the procedural

equipment was prepared, healthcare workers left the operating room, and automatic spraying of the antineoplastic drug began. After each antineoplastic drug was sprayed inside the abdominal cavity, workers waited outside the operating room for about 35 minutes while the drug dispersed and penetrated within the peritoneum. After about 35 minutes, healthcare workers entered the operating room and released the air pressure inside the abdominal cavity through an air-waste system equipped with a glass microfiber filter impregnated with a carbon layer (Model: Laparo Clear Smoke Filtration Kit, pore size 0.027 μm, diameter 50 mm, GVS Inc., Italy) (**Figure 1**).

Typically, seven healthcare workers performed the PIPAC procedure. They included the veterinarian providing anesthetic to the swine, the surgeon, nursing assistant, three nurses preparing the antineoplastic drug, and an engineer controlling the PIPAC device.

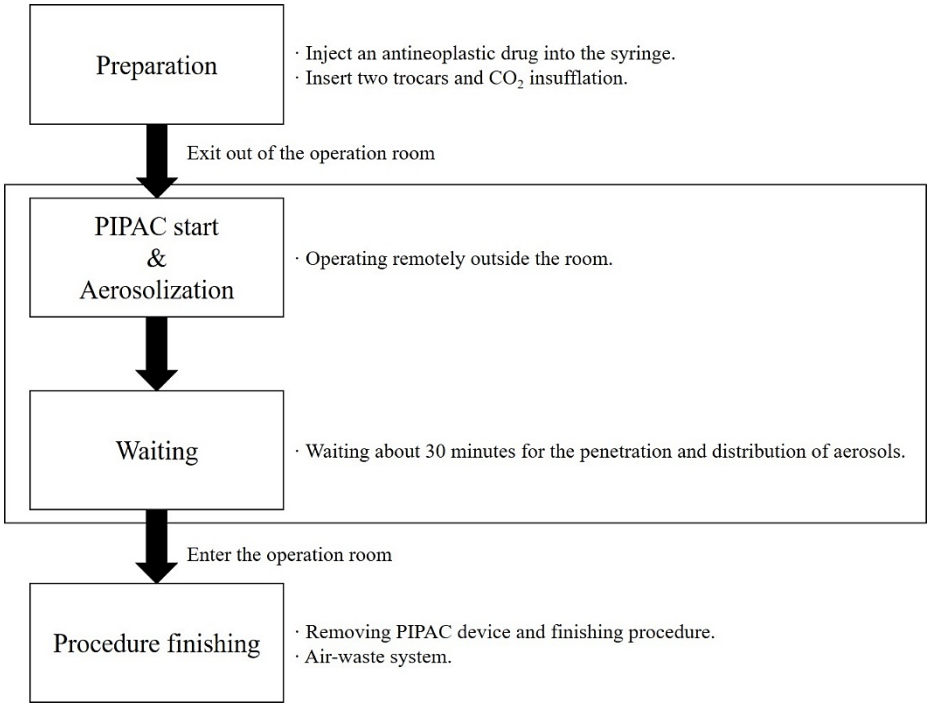

Figure 1. The outline of PIPAC procedure.

2.2. Sampling and analysis

2.2.1. Operating room conditions

The temperature and relative humidity of the operating room were centrally controlled for the building and measured using a thermohygrometer (Model: TR-72Ui, T&D Inc., Japan).

To analyze the ventilation system, the supply and exhaust air in the operating room were checked after completion of the experiment. The flow rate (m^3/sec) of the air exhaust outlet was measured using a direct-reading balometer (Model: Alnor EBT-731, TSI Inc., Shoreview, MN, USA). Because the area (m^2) of the air supply outlet was larger than the balometer could measure, air velocity at the supply outlet was obtained using an air velocity meter (Model: Veloci-CALC 9545, TSI Inc., Shoreview, MN, USA), and the flow rate was calculated by multiplying the air velocity (m/sec) by the area (m^2). A smoking test was performed at the entrance of the operating room and at the site of trocar insertion to evaluate the positive/negative pressure status.

2.2.2. Surface sampling of PIPAC device and protective equipment

Surface sampling was conducted using a wiping method with filter paper (Model: Whatman 42, ashless, diameter 55 mm, GE Healthcare Life Science, USA), as described in a previous study (Turci et al., 2003). Prior to sampling, the filter papers were pretreated. The papers were wetted with a wiping solution consisting of 10% acetonitrile, 25% methanol, and 65% Milli-Q water buffered to pH 6.0 (Connor et al., 2010).

In addition to the personal protective equipment used by the healthcare workers, other sites where contamination was possible were selected for surface sampling. These sites were located around the PIPAC devices, including the trocar, telescope, and spraying nozzle (**Figure 3**). After use, the spraying nozzle were cleaned four to five times with cotton soaked in 70% ethanol, and were wiped before and after cleaning. Cleaning was conducted after the PIPAC procedure was finished. To evaluate the surface contamination level of the protective equipment, we obtained the masks, gloves, and shoes of the healthcare workers fulfilling two roles (surgeon, nurses). The anesthesiologist was excluded from equipment analysis because the swine were anesthetized prior to the start of the PIPAC procedure.

The selected sites were wiped over an area of 10 × 10 cm on flat surfaces and in a manner to obtain the maximum area (cm^2) on uneven surfaces (Connor et al., 2016). As the first step of the sampling strategy, the whole wetted filter was first wiped over the target area, then folded in half and wiped (second half-filter)

in the opposite direction, and finally folded in half again and wiped again in the first direction (third half-filter). The finished filter was folded and placed in a 50-ml vial, which was stored at a low temperature (about -4 C) and transported to the laboratory to prevent sample loss due to the risk of evaporation at room temperature (**Figure 2**).

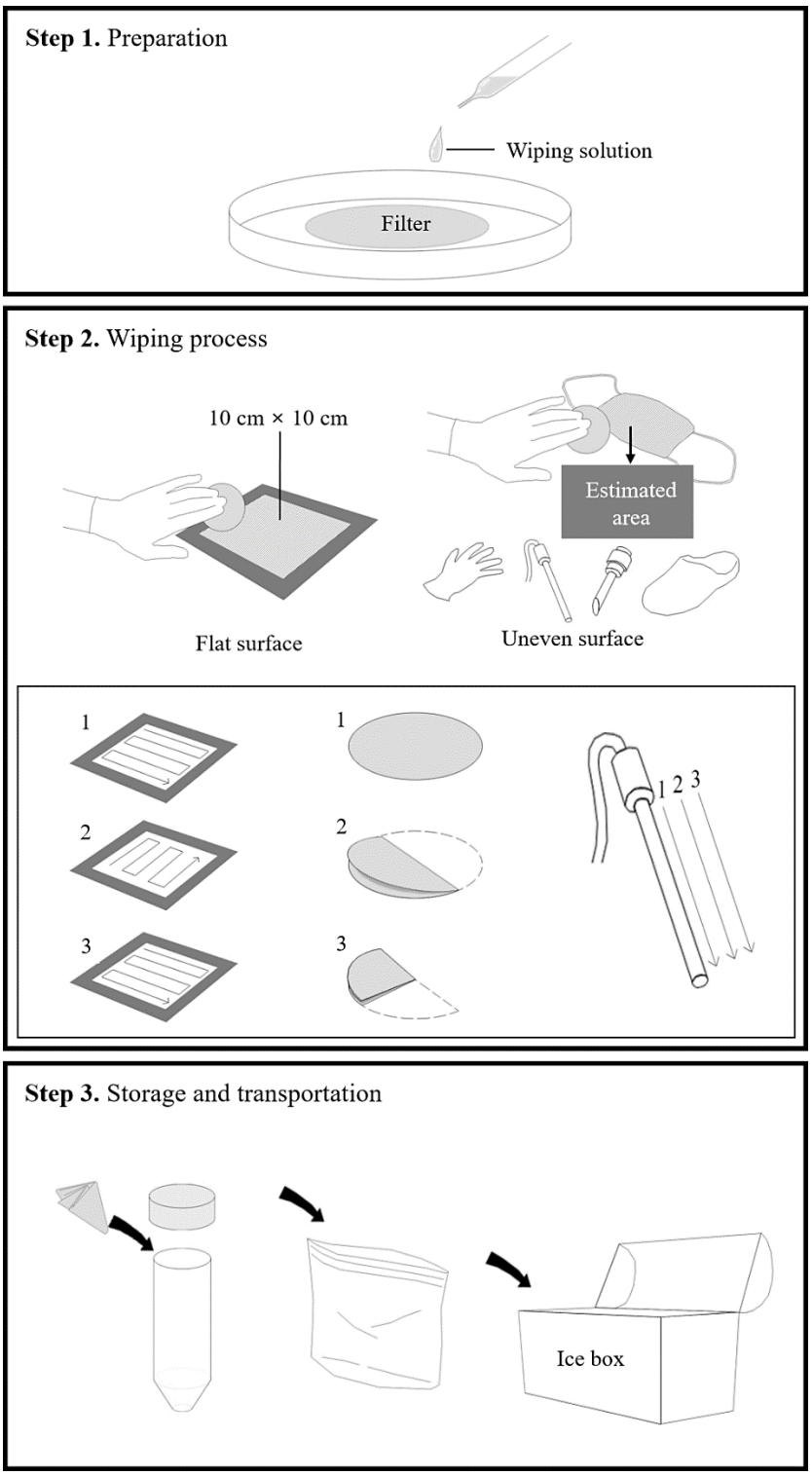

Figure 2. The procedures of wipe sampling.

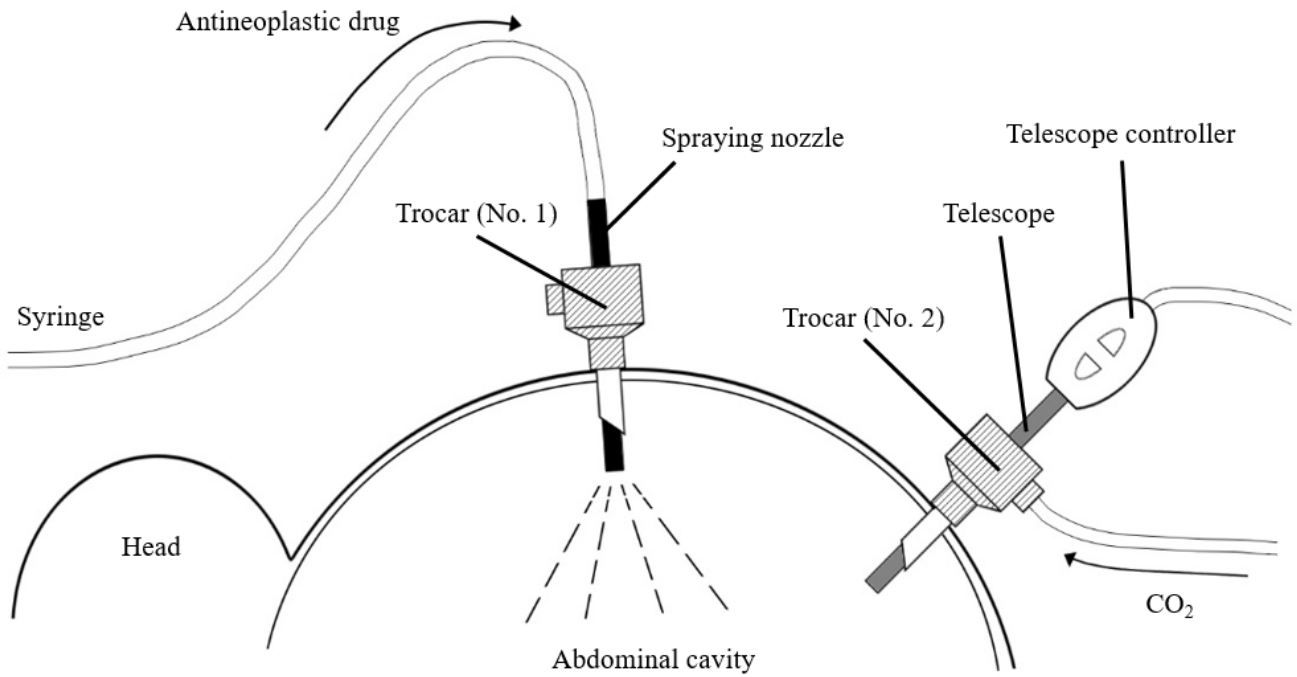

Figure 3. The section of PIPAC operation on the swine. Surface sampling sites (colored and lined) were trocar (Nos. 1, 2), telescope and spraying nozzle.

2.2.3. Air sampling

Air samples for measurement of the three drugs (paclitaxel, cisplatin, and doxorubicin) were collected with a Zefluor filter (diameter 37 mm, pore size 1.0 μm, supported by polytetrafluoroethylene [PTFE]; Pall Life Science, USA), mixed cellulose ester membrane filter (MCE, diameter 37 mm, pore size 0.8 μm, SKC Inc., Eighty Four, PA, USA), and nitrocellulose membrane filter (diameter 47 mm, pore size 0.45 μm, GVS life science, Italy), respectively (Larson, 2001). For cisplatin, an MCE filter was used for sampling to trace platinum, according to the National Institute for Occupational Health and Safety (NIOSH) Manual of Analytical Methods (NMAM) protocol 7300 (Turci et al., 2003).

This method used a high-flow pump sampler (Model: SARA-5100, KEMIK corp., Republic of Korea) at a flow rate of approximately 17–18 L/min. This method ensured the maximum flow rate possible by employing a sampling volume below the LOD of previous studies (Willaert et al., 2017; Ametsbichler et al., 2018). The flow rate was calibrated using an airflow calibrator (Model: Bios Drycal, Mesa Laboratories, Lakewood, CO, USA) before and after measurement.

Air sampling was conducted at the locations where healthcare workers were stationed during the procedure (**Figure 5**). Sampled individuals around the operating table (surgeon, nurse, and anesthesiologist) were selected according to their tasks related the PIPAC surgical procedure. Air was also collected at the left corner of the entrance to the operating room. The

measured height was about 1.5 m from the floor, considered the breathing zone of the healthcare workers. Sampling time was about 50 ± 5 minutes, including during preparation of drugs, injection into the syringe, and air-waste management.

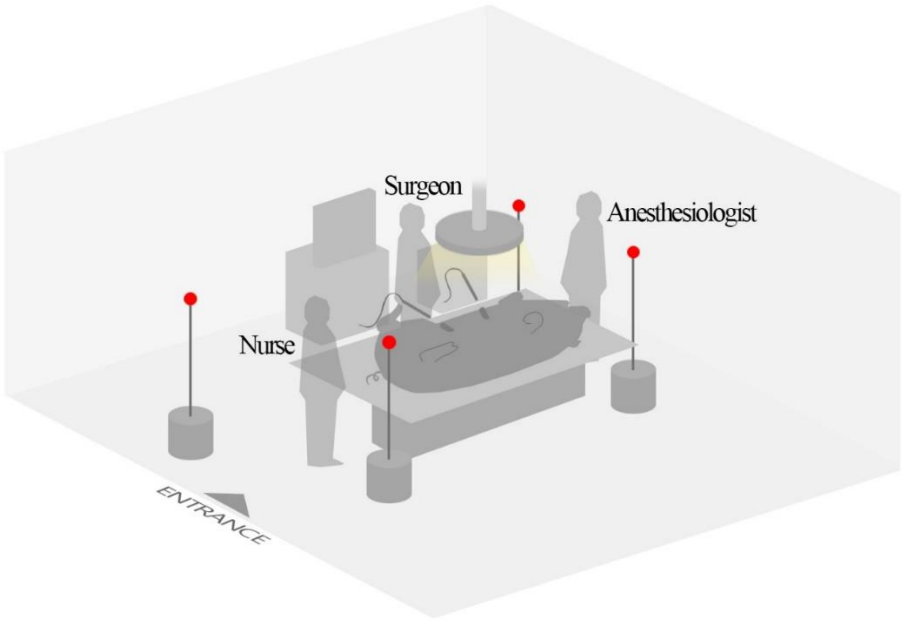

Figure 4. The outline of air sampling locations.

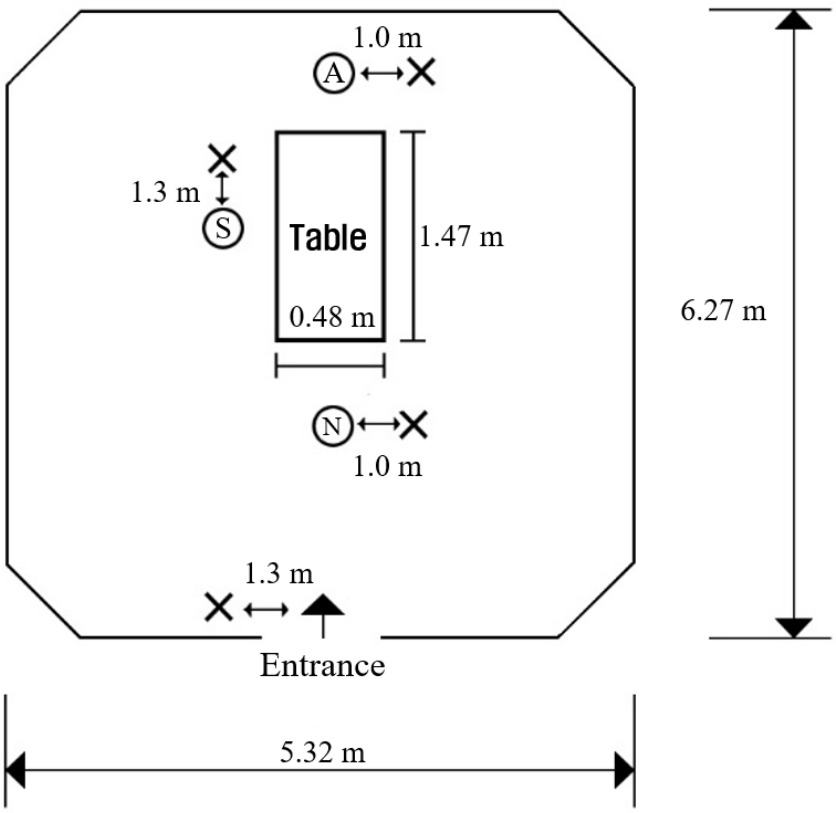

Figure 5. The plan of air sampling locations and dimension lines (S, surgeon; A, anesthesiologist; N, nurse).

2.2.4. Sample analysis

Analytical methods for quantitative analyses were selected depending on the type of filter. A stock solution of doxorubicin was dissolved in 50% methanol (Purity: >99.9%, HPLC grade, Burdick & Jackson, MI, USA) to 1 mg/ml and then diluted with 100% methanol to prepare a standard solution. The prepared standard solution was diluted to 5, 10, 20, 50, and 100 ng/ml to construct a linear calibration curve. Each sample collected for doxorubicin analysis, including used nitrocellulose filters and Whatman filter paper, was placed in a 50 ml tube, extracted with 10 ml methanol, and then subjected to sonication for 1 hour (Larson et al., 2003; Christine et al., 2013). Centrifugation was carried out at 12,000 rpm for 5 minutes to collect the supernatant. Then, 2 μl aliquots of each sample were injected into the ultra-high-performance liquid chromatograph (HPLC-MS/MS, Model: Nexera X2, Shimadzu Scientific Corp., Japan) under the analysis conditions shown in **Table 1**. The column used for HPLC-MS/MS was an ACQUITY BEH C18 (1.7 μm, 50×2.1 mm, Agilent Technologies Inc., USA), and the quantification mode was performed using the multiple reaction monitoring (MRM) mode. The detection ion mode of the mass spectrometer was positive ion mode. All samples were analyzed at least three times, and the average value was calculated.

For analysis of paclitaxel, the standard solution was diluted to 5, 10, 20, 50, and 100 ng/ml to construct a linear calibration curve. Collected samples of Zefluor filter and Whatman filter paper were extracted with 10 ml of acetonitrile (Purity: >99.9%, HPLC grade, Merck, Germany) and subjected to

sonication for 1 hour. Centrifugation was carried out at 4,000 rpm for 10 minutes to collect the supernatant. An injection volume of 1 μl extracted from each sample was injected into the ultra-high-performance liquid chromatograph (HPLC-MS/MS, Model: Xevo TQ-XS triple quadrupole MS, Milford, MA, Waters Corp., USA) under the analysis conditions shown in **Table 1**. The same column was used as for analysis of doxorubicin, and the mass spectrometer and quantification modes were electron spray ionization (ESI) and MRM, respectively (**Table 1**) (Larson et al., 2003; Pretty et al., 2012).

To analyze platinum as a surrogate for cisplatin, we referred to NMAM 7300. A microwave (Model: MARS 6, CEM Corp., Matthews, NC, USA) was used for preprocessing. The air samples were placed in a microwave vessel with 3 ml of 70% nitric acid (Sigma Aldrich, MO, USA). The temperature of the microwave was gradually raised to 200°C for 15 minutes and then maintained for 15 minutes. The pressure was set to 800 psi, and the power to 900–1050 W. For wipe samples, 5 ml of nitric acid was injected into the microwave vessel. The temperature was gradually raised to 180°C for 15 minutes and then maintained for 10 minutes. The pressure and power were the same as those for air samples. The extracted samples were brought up to 40 ml with distilled water and analyzed using an inductively coupled plasma mass spectrometer (ICP-MS, Model: NexION 350D, Perkin Elmer Inc., Houston, TX, USA) (**Table 2**).

2.2.5. Quality assurance

The LOD for each of the three antineoplastic drugs was calculated in a different way. For the LOD of doxorubicin, the standard deviation of the intercept divided by the mean of the slope was determined from the linear regression of standard solution dilutions (correlation coefficient, r^2: 0.9984–0.9997) and multiplied by 3.3 to account for MRM mode. Paclitaxel and platinum LODs were three standard deviations from measurement of seven replicates at the lowest level of the standard solution, which was 1 or 5 ng/ml. These two drugs showed linearity, with a correlation coefficient (r^2) for paclitaxel of 0.9985–0.9999 and for platinum of 0.9999–1.0000. The LODs of the three antineoplastic drugs were determined as follows: paclitaxel 36.5 ng/sample, platinum 0.37 ng/sample, doxorubicin 12.8 ng/sample.

2.3. Data analysis

We calculated descriptive statistics using a statistical software program (SPSS ver. 25, IBM Corp., USA) for all data. Normality was assessed with the Shapiro–Wilk test, and the data showed a lognormal distribution. To calculate the geometric mean (GM) and geometric standard deviation (GSD), non-detected values were set to 1/2 LOD divided by the average air volume sampled for data analysis (Hornung & Reed, 1990). The Kruskal–Wallis rank test was used to compare surface concentrations among protection equipment types such as masks, gloves, and shoes, and also to compare air locations.

Table 1. The conditions of LC-MS/MS analyzed paclitaxel, doxorubicin

Parameter		Analytical conditions	
Analyte		Paclitaxel	Doxorubicin
Used column		ACQUITY BEH C18, 1.7 μm, 50 × 2.1 mm	ACQUITY BEH C18, 1.7 μm, 50 × 2.1 mm
Flow rate (ml/min)		0.6	0.4
Oven temperature (℃)		40	40
Mobile phase	A	0.1% formic acid / water	0.1% formic acid / water
	B	0.1% formic acid / acetonitrile	0.1% formic acid / acetonitrile
Injection volume (μl)		1	2
Quantification mode		MRM mode	MRM mode
Ionization mode		Electron Spray Ionization (ESI)	Positive ion mode
Retention time (min)		0.3	1.8
Precursor ion (m/z)		876.1	544.3
Product ion (m/z)		308.0	397.1

Table 2. The conditions of ICP-MS analyzed platinum of cisplatin

Parameter		Analytical conditions
Nebulizer		Concentric glass nebulizer
Spray chamber		Glass cyclonic spray chamber
RF generator		Power output: 500 W – 1,600 W
Argon Flow rate	Plasma gas (L/min)	18.00
	Auxiliary gas (L/min)	1.20
	Nebulizer gas (L/min)	0.96
Sampler cone (mm)		Nickel 1.0
Skimmer cone (mm)		Nickel 0.9
Hyper-Skimmer cone (mm)		Aluminum alloy 1.0
Vacuum	Interface (torr)	$< 2 \times 10^{-6}$
	Quadrapole (torr)	$< 3 \times 10^{-8}$
Data acquisition		Peak hopping, 1 reading, 20 sweep, 3 replicate
Measurement mode		Quantification mode

3. Results

3.1. Operating room conditions for PIPAC

The volume of the operating room was about 98.1 m^3 (5.3×6.3×2.9 m). The operating room contained two air supply vents in the ceiling, with four exhaust outlets located at each corner. The area of each air supply vent was about 0.6 m^2 (0.6×0.9 m), and that of each exhaust vent was about 0.1 m^2 (0.2×0.4 m).

The flow rate of the air supply and exhaust were 30.2 m^3/min and 15.1 m^3/min, respectively. The air supply flow rate was higher than that of the exhaust, and the smoking test showed that the operating room maintained positive pressure relative to the corridor. When we measured the velocity at the slit in the closed entrance to the corridor, the velocity of the airflow was about 1.7 m/sec. In addition, because pressure in the abdominal cavity was maintained through insufflation, we measured the velocity around the insertion sites of the two trocars (Nos. 1, 2) to check for possible leakage. The measured velocity was zero, indicating no airflow.

The temperature and relative humidity were controlled through a centralized system for the building. Measurements taken during the operation showed an average relative humidity of 40.5% and average temperature of 22.7°C. The temperature was similar to the set value of 22°C, but the relative humidity was below the set value of 50% (**Table 3**).

Table 3. The information on PIPAC condition of operating room

Antineoplastic drug	No.	No. of swine	No. of samples air / wipe (all)	Temperature [a] (℃)	Relative humidity [a] (%)	Air supply [b] (m^3/min)	Air exhaust [b] (m^3/min)
Paclitaxel	1	1	4 / 10 (14)	22.7 ± 1.7	39.5 ± 17.4	30.2	15.1
	2	1	4 / 10 (14)				
	3	3	4 / 19 (23)				
	Sub total	5	12 / 39 (51)				
Cisplatin	4	1	4 / 7 (11)	22.8 ± 0.5	40.9 ± 5.1		
	5	1	4 / 10 (14)				
	6	2	4 / 13 (17)				
	7	2	4 / 14 (18)				
	Sub total	6	16 / 44 (60)				
Doxorubicin	8	1	4 / 2 (6)	22.0 ± 2.0	50.0 ± 5.0		
	9	1	4 / 2 (6)				
	10	3	12 / 3 (15)				
	11	2	8 / 11 (19)				
	Sub total	7	28 / 18 (46)				
Total		18	56 / 101 (157)	22.7 ± 1.2	40.5 ± 12.5	30.2	15.1

***Note*:** The air velocity of a slit around the closed entrance doors was about 1.7 m/sec.

[a] Temperature and relative humidity were controlled the centralized management, and the set values were 22℃ and 50%, respectively.

[b] The air supply and exhaust rate have been separately measured after the finished of the PIPAC procedures.

3.2. Surface contamination of PIPAC devices

Surface samples from the PIPAC devices, divided into trocar (Nos. 1, 2), telescope, and spraying nozzle (before and after cleaning), showed contamination with paclitaxel and cisplatin, but not with doxorubicin (**Table 4**).

For paclitaxel, the concentration of all surface samples was above the LOD. The surface concentration of paclitaxel was highest in the spraying nozzle before cleaning (GM, 4.95 ng/cm^2), followed in order by the telescope (GM, 3.87 ng/cm^2), trocar 1 (GM, 2.81 ng/cm^2), trocar 2 (GM, 0.70 ng/cm^2), and the spraying nozzle after cleaning (GM, 0.66 ng/cm^2). The spraying nozzle before cleaning, which was directly exposed to the antineoplastic drug in the peritoneum, was in the range of 0.76–76.75 ng/cm^2. The concentration at trocar 1, which was used to insert and remove these spraying nozzles, was in the range of 0.50–55.30 ng/cm^2. The trocar 2, used for inserting the telescope, had relatively low contamination (0.46–1.04 ng/cm^2), and the telescope inserted into the abdominal cavity measured up to 10.76 ng/cm^2. Comparison of the results for the spraying nozzle inserted into the abdominal cavity before and after cleaning confirmed that the nozzle was less contaminated after cleaning (GM, 0.66 ng/cm^2) than before cleaning (GM, 4.95 ng/cm^2).

Platinum was measured above the LOD in all wipe samples (n = 23), with a range of 0.02–235.09 ng/cm^2. Curiously, the location with the highest measured level of platinum was trocar 2 (GM, 5.55 ng/cm^2). The GM of trocar 1, the telescope, the nozzle before cleaning, and the nozzle after cleaning were 4.80 ng/cm^2, 3.90 ng/cm^2, 2.43 ng/cm^2, and 0.31 ng/cm^2, respectively. The range on

trocar 2 was 0.08–235.09 ng/cm^2; this value was affected by one detection of 235.09 ng/cm^2. Platinum was found to be elevated in both trocars (No. 1, 2) inserted into the abdomen relative to the telescope and spraying nozzle, which were inserted into the abdominal cavity and exposed directly to the drug.

Fewer samples of doxorubicin than of the other two drugs were collected (n = 10), but 3 of the 10 samples were above the LOD. The range of detected concentrations was from below the LOD to 3.86 ng/cm^2, and the GM (0.42 ng/cm^2) of the three samples was lower than those of the other two drugs (paclitaxel GM, 1.94 ng/cm^2; platinum GM, 2.14 ng/cm^2).

Table 4. The surface concentration in the devices of three antineoplastic drugs during PIPAC procedure

Unit: ng/cm^2

Sampling location	Paclitaxel			Platinum (cisplatin)			Doxorubicin		
	No. of <LOD/ sample	GM (GSD)	Range	No. of <LOD/ sample	GM (GSD)	Range	No. of <LOD/ sample	GM (GSD)	Range
Trocar 1[a]	0/5	2.81 (8.56)	0.50 – 55.30	0/3	4.80 (1.42)	3.21 – 6.00	2/2	–	< LOD
Trocar 2[a]	0/3	0.70 (1.50)	0.46 – 1.04	0/3	5.55 (55.07)	0.08 – 235.09	1/1	–	< LOD
Telescope	0/4	3.87 (2.61)	1.17 – 10.95	0/6	3.90 (3.14)	1.68 – 35.90	4/7	0.17 (4.60)	< LOD – 3.86
Nozzle (before cleaning)	0/3	4.95 (11.34)	0.76 – 76.75	0/6	2.43 (2.00)	1.19 – 8.94	–	–	–
Nozzle (after cleaning)	0/4	0.66 (2.10)	0.39 – 1.92	0/5	0.31 (12.18)	0.02 – 5.12	–	–	–
Total	0/19	1.94 (5.12)	0.39 – 76.75	0/23	2.14 (7.73)	0.02 – 235.1	7/10	0.42 (8.93)	< LOD – 3.86

***Abbreviations*:** LOD, Limit of detection; GM, Geometric mean; GSD, Geometric standard deviation; –, No measurement; Min, Minimum; Max, Maximum.
***Note*:** (1) The LOD of the three antineoplastic drugs as follow: paclitaxel, 36.5 ng/sample; platinum, 0.37 ng/sample; doxorubicin, 12.8 ng/sample.
(2) GM and GSD were calculated using 1/2 LOD.
[a] The trocar 1 injected the spraying nozzle, the trocar 2 inserted the telescope combined with CO_2 insufflation nozzle.

3.3. Contamination of protective equipment in healthcare workers

Paclitaxel and platinum were detected in staff safety equipment, but not doxorubicin. Paclitaxel was detected in 18 of 20 samples (90%), and platinum in 18 of 21 (about 86%). The only protective equipment collected that was used in the doxorubicin procedure was the gloves (n = 4) and shoes (n = 4) worn by the surgeon; no contamination was detected.

To compare concentrations among the three equipment types, the Kruskal–Wallis rank test was used. No significant differences in paclitaxel levels were observed among the three equipment types used by the surgeon (p = 0.057). However, the mask (GM, 0.59 ng/cm^2) had higher levels than the gloves (GM, 0.19 ng/cm^2) and shoes (0.13 ng/cm^2), and the concentration range of the gloves was the largest (0.09–0.34 ng/cm^2). Similarly, when cisplatin was used by the surgeon, the concentration levels of platinum on the three equipment types showed no significant difference (p = 0.123). However, the platinum concentration on equipment was lowest on shoes (GM, <0.01 ng/cm^2), while the mask (GM, 0.05 ng/cm^2) and gloves (GM, 0.06 ng/cm^2) were similar.

In terms of paclitaxel exposure for the nurse, the concentration on the mask (GM, 0.58 ng/cm^2) was similar to that on the surgeon's mask (GM, 0.59 ng/cm^2), but the gloves (GM, 0.07 ng/cm^2) and shoes (GM, 0.09 ng/cm^2) had lower levels than those of the surgeon. Significant differences were observed among the nurses three equipment items (p = 0.042). In the procedure using cisplatin,

the platinum concentration levels on the nurse's protective equipment were similar to those for the surgeon, and no significant differences was found among equipment types ($p = 0.067$) (**Table 5**).

Table 5. The surface concentration in the equipment of three antineoplastic drugs during PIPAC procedure

Unit: ng/cm^2

Job	Type	Paclitaxel				Platinum (cisplatin)			
		No. of < LOD /sample	GM (GSD)	Range	p-value [a]	No. of < LOD /sample	GM (GSD)	Range	p-value [a]
Surgeon	Mask	0 / 3	0.59 (1.04)	0.57 – 0.62	0.057	1 / 4	0.05 (9.20)	< LOD – 0.22	0.123
	Gloves	0 / 4	0.19 (1.91)	0.09 – 0.34		0 / 4	0.06 (3.14)	0.02 – 0.23	
	Shoes	0 / 3	0.13 (1.01)	0.13 – 0.13		1 / 4	< 0.01 (5.90)	< LOD – 0.02	
Nurse	Mask	0 / 3	0.58 (1.00)	0.58 – 0.58	0.042	0 / 3	0.06 (1.63)	0.03 – 0.08	0.067
	Gloves	1 / 4	0.07 (1.89)	< LOD – 0.10		0 / 3	0.04 (2.04)	0.02 – 0.09	
	Shoes	1 / 3	0.09 (2.01)	< LOD – 0.13		1 / 3	< 0.01 (5.56)	< LOD – 0.01	
Total		2 / 20	0.51 (6.02)	< LOD – 0.62		3 / 21	0.02 (6.81)	< LOD – 0.23	

***Abbreviations*:** LOD, Limit of detection; GM, Geometric mean; GSD, Geometric standard deviation; Min, Minimum; Max, Maximum; -, No data.
***Note*:** (1) The LOD of the three antineoplastic drugs as follow: paclitaxel, 36.5 ng/sample; platinum, 0.37 ng/sample; doxorubicin, 12.8 ng/sample. (2) GM and GSD were calculated using 1/2 LOD. (3) All collected samples of doxorubicin were below the LOD (n=8).
[a] Kruskal-wallis rank test.

3.4. Airborne levels of each antineoplastic drug during PIPAC procedures

During the PIPAC procedures, paclitaxel (n = 12) was detected in the air, whereas cisplatin (n = 16) and doxorubicin (n = 18) were not detected (**Table 6**).

The range of paclitaxel detected was from below the LOD to 87.81 ng/m^3 (GM, 42.05 ng/m^3; GSD, 1.74). One sample below the LOD was detected at the surgeon's position, and the others were from nurse and the left side of the entrance, respectively. The sample from the left side of the entrance was collected during the second procedure, whereas the other two samples (from the positions of the surgeon and nurse) were obtained during the third procedure. Samples that measured below the LOD affected calculation of the GM. The GM at these three positions (surgeon, nurse, and left of the entrance) were 38.79 ng/m^3, 38.18 ng/m^3, and 37.29 ng/m^3, respectively, which were lower than that for the anesthesiologist (56.60 ng/m^3). No significant differences were found among these four locations (p = 0.551).

All samples of doxorubicin and platinum were below the LOD, although they were collected under the same conditions as the paclitaxel samples.

Table 6. The air concentration of three antineoplastic drugs during PIPAC procedure

Unit: ng/m^3

Sampling location	Paclitaxel [a]		
	No. of < LOD / sample	GM (GSD)	Range
Surgeon	1 / 3	33.55 (2.45)	< LOD – 87.81
Nurse	1 / 3	33.04 (2.44)	< LOD – 86.64
Anesthesiologist	0 / 3	56.60 (1.85)	27.96 – 86.74
Left of the entrance	1 / 3	31.11 (2.24)	< LOD – 73.90
Total	3 / 12	37.38 (2.10)	< LOD – 87.81

***Abbreviations*:** LOD, Limit of detection; GM, Geometric mean; GSD, Geometric standard deviation; Min, Minimum; Max, Maximum.

***Note*:** (1) The LOD of the three antineoplastic drugs as follow: paclitaxel, 36.5 ng/sample; platinum, 0.37 ng/sample; doxorubicin, 12.8 ng/sample. (2) GM and GSD were calculated using 1/2 LOD. (3) All collected samples of cisplatin (n=16) and doxorubicin (n=28) were below the LOD.

[a] Kruskal-Wallis rank test ($p > 0.05$).

4. Discussion

Occupational exposure to three antineoplastic drugs (paclitaxel, cisplatin, and doxorubicin) via surface and airborne contamination was evaluated during PIPAC. Although there have been fewer studies on occupational exposure than pre-clinical and clinical studies, several studies have reported contamination of surfaces and air (Grass et al., 2017). Air concentrations have been measured below the LOD for some antineoplastic drugs (doxorubicin, platinum compound) since the development of PIPAC in Europe. However, in this study, we identified contamination with paclitaxel in the air and with two drugs (paclitaxel, platinum) on surfaces (Solaß et al., 2013).

This study was conducted under the same conditions and protocol as the clinical procedure, and the PIPAC was employed on swine as an animal model (Tempfer et al., 2014; Khosrawipour et al., 2016). The evaluation of surface and air contamination in this study might have benefits aside from its application to patients. In particular, the detection of paclitaxel in the air was important, as it could increase the inhalation risk of exposure for the patient and healthcare workers in the operating room (Nardiradze et al., 2016). In this study, preparation and injection of the antineoplastic drugs into the syringe were conducted in the operating room, whereas in the actual procedure, the drugs should be provided to healthcare workers in a finished form that is mixed and diluted and placed in a syringe. Dermal exposure is a possibility during the process of preparation, handling, and disposal of the antineoplastic drug (Pabst & Tempfer, 2018).

Several studies conducted on occupational exposure and safety for the PIPAC procedure since 2013 have generally evaluated only platinum contamination on surfaces and in the air. Doxorubicin was the most commonly used antineoplastic drug for clinical PIPAC procedures, but only platinum was monitored. Limited studies have examined exposure to paclitaxel and doxorubicin associated with PIPAC (**Table 7**).

Surface contamination related to PIPAC was reported in 2017 in an evaluation of numerous locations, gloves, and surgeons' hands. That research showed that platinum contamination at all sites was below the LOD during and after two clinical PIPAC procedures (Willaert et al., 2017). Another study reported substantial contamination of PIPAC devices (i.e. injector, syringe and trocar). In fact, the upper part of the trocar, including the spraying nozzle and telescope, tended to be stained with drug droplets directly, making it a potential risk for contamination (Ametsbichler et al., 2018). Likewise, the PIPAC devices in this study were a risk for contamination, as their platinum levels were above the LOD (range, 0.02 to 235.1 ng/cm^2) (**Table 4**).

Moreover, previous research has reported heavy platinum contamination on the surgeon's outer gloves, which has been attributed to leaks during the surgeon's tasks such as removal of the contaminated trocar and closure of the laparoscopic incisions (Ndaw et al., 2018). In this study, it is likely that the surgeon's protective equipment was exposed to the antineoplastic drug, as the tasks performed were similar, including handling of devices (trocar, telescope, and spraying nozzle). Most devices and equipment samples used with paclitaxel

appeared to follow this pattern. In particular, on the surgeon's and nurse's masks, relatively high concentrations (GM, 0.59 ng/cm^2, 0.58 ng/cm^2, respectively) were detected, indicating airborne contamination (**Table 5**).

Monitoring of airborne contamination during the PIPAC procedure was first undertaken in 2013. All studies on airborne levels during PIPAC have shown that cisplatin (platinum) samples were always below the LOD, indicating that the risk of airborne contamination during PIPAC was low. Furthermore, most authors have supported the safety of the PIPAC procedure, as long as no specific event (e.g., leakage) occurs (Ametsbichler et al., 2018). However, because research into inhalation exposure to other drugs (e.g., paclitaxel) is limited, these opinions are based only on evaluation of platinum contamination.

In this study, paclitaxel was detected in 9 of 12 samples (GM, 37.38 ng/m^3; range, below LOD to 87.81 ng/cm^3) (**Table 6**). There are many explanations for the detection of only paclitaxel in the air. This study presents the first exposure assessment of the combination of PIPAC and precessional motion. It remains unclear whether leakage of paclitaxel from the abdominal cavity is affected by precessional motion, as two of the drugs (doxorubicin, cisplatin) for which this motion is used were not detected in the air of the surrounding environment. Another factor that should be explored is the physicochemical properties of the drugs. Paclitaxel (Taxol) is known to be lipophilic, and doxorubicin and cisplatin are water soluble (Larson, 2001, Larson et al., 2003; Turci et al., 2003). In addition, the biopharmaceutics classification system (BCS) places paclitaxel in Class IV, indicating low aqueous solubility, poor permeability, and poor

absorption, especially in the gastrointestinal tract (Ghadi & Dand, 2017). For this reason, paclitaxel sprayed at high pressure during the PIPAC procedure might not penetrate and be absorbed into the cells of the peritoneum, instead remaining in the aerosol form in the abdominal cavity. If this is the case, several leakage routes into the air are possible. First, paclitaxel remaining in the peritoneum might leak through the gap around the inserted trocar. Second, when spaying is finished, aerosolized paclitaxel in the abdominal cavity could leak from any loose connections in the tubes between the trocar and the filter of the air-waste system.

These three antineoplastic drugs are commonly known as cytotoxic drugs. They have been reported to have carcinogenic, mutagenic, and teratogenic effects in animals (WHO, 2013). The oral LD_{50} of doxorubicin was reported as 570 mg/kg in mouse, and that of cisplatin as 32 mg/kg in mouse and 20 mg/kg in rat (Solaß et al., 2013). It is difficult to directly compare the present results with these values. Nevertheless, because surface contamination has been identified, specific safety and health protocols within the procedure should be established and followed to minimize occupational exposure to antineoplastic drugs. Data for inhalation toxicity in humans was difficult to find for all three drugs. Several countries have established occupational exposure limits. In the US, the Occupational Safety and Health Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), and American Conference of Governmental Industrial Hygienists (ACGIH) have limited cisplatin to 0.002 mg/m^3 as platinum (time-weighted average, TWA) (Murff,

2012). In the Netherlands, the additional lifetime cancer risk level of 4×10^{-5} for 40 years of occupational exposure was set at 0.05 μg/m^3, but no standard for cisplatin in PIPAC has been established in Germany (DECOS, 2005). In Korea, the TWA proposed by ACGIH (0.002 mg/m^3) has been applied. Even though specific risk characterization has been limited, the present study suggests the possibility of exposure through certain routes, and shows the necessity of preventive measures.

This study has several limitations. First, we did not evaluate contamination of the floor and area around the operating table, which were sampled in previous studies. However, the concentration levels on devices inserted into the abdominal cavity and directly exposed to the antineoplastic drug aerosol were evaluated, which suggested potential exposure of healthcare workers.

Second, the number of samples for each of the three drugs was inconsistent. In particular, few surface samples showed doxorubicin contamination. The PIPAC procedure using doxorubicin was the pilot experiment, and we selected many surface sampling sites. However, all surface samples were below the LOD. The sample with the highest concentration was collected after a leakage event at the connection of the syringe (**Table A-1**). Therefore, we developed and updated the methodology for selection of surface locations with greater probabilities of detection.

Although studies on a standardized method of paclitaxel sampling and analysis are underway, we referred to established methodology for sampling media, extraction solutions, recovery procedures, and other details of the

evaluation of airborne paclitaxel (Sotani et al., 2000; Connor et al., 2010; Pretty et al., 2012; Jeronimo et al., 2015). A standardized method is a necessity for future research.

Currently, research on safety protocols for preventing occupational exposure related to the PIPAC procedure is underway (Pabst & Tempfer, 2018). Efforts are also being made to establish safe surgical procedures. In this study, contamination of the spraying nozzles inserted into the abdominal cavity and the trocars was detected. We recommend that these devices be considered disposable items; furthermore, the telescope should be cleaned several times. Moreover, contamination was detected not only on gloves but also on masks and shoes, and appropriate protective equipment should be selected. Considering that paclitaxel was detected in the air, further control measures for this drug should be implemented. This study could be used to provide information for development of more specific safety procedures.

Table 7. Summary of previous studies on exposure assessment for PIPAC procedure

Reference	Used A.D.	Target A.D.	Subject	Objective	Methods	Key finding(s)
Solaß et al., (2013)	DX, CP (Pt)	Pt	2 Patients	- To identify and evaluate potential hazards concerning occupational exposure during PIPAC procedure in the real clinical conditions and to the human patient.	***PIPAC conditions*** - Temp. : 22.3 to 22.6°C; R.H. : 36 to 37 % - Abdominal pressure: 12 to 15 mmHg - Spraying flow rate: 30 ml/min - Laminar flow in O.R. ***Exposure assessment*** - Cellulose nitrate filter (diameter, 50 mm) - Flow rate: 22.5 m^3/hr - LOD (pt): 9 ng/m^3	***Airborne contamination*** - All cisplatin samples were detected below the LOD at the working positions of the surgeon and the anesthesiologist under real PIPAC conditions.
Graversen et al., (2016)	DX CP (Pt)	Pt	2 Patients	- To measure the presence of airborne platinum particles in O.R. room during PIPAC.	***PIPAC conditions*** - Temp. : 20°C; R.H. : 55% - Abdominal pressure: 12 mmHg ***Exposure assessment*** - Cellulose filter (diameter, 37 mm) - Flow rate: 1.9 L/min - Inductively coupled plasma mass spectrometry (ICP-MS) - LOD (pt): 0.01 ng/sample	***Airborne contamination*** - The filters showed no traces of platinum. - The chemotherapy particles in the air is probably limited. - Our data are in agreement with safety data from other PIPAC studies.

Willaert et al., (2017)	DX, CP (Pt), OX (Pt)	Pt	2 Patients	- To report an additional, comprehensive toxicological analysis including air and surface samples after clinical PIPAC procedures using cisplatin/doxorubicin and oxaliplatin.	***PIPAC conditions*** - Temp. : 20°C; R.H. : 55% - Spraying flow rate: 30 ml/min - Laminar flow in O.R. ***Exposure assessment*** - IOM-samplers (PTFE; diameter, 25 mm) - Flow rate: 2.0 L/min - Wipe Kits (17 ml of 0.05M HCl dropped surface) - Inductively coupled plasma mass spectrometry (ICP-MS) - LOQ (pt): 4, 27 ng/cm^2 (air), 50 to 70 ng/sample (wipe)	***Surface & Airborne contamination*** - The results have shown that the platinum was unable to detect any surface (floor surgeon, floor drug administration, floor drug suction equipment, floor anesthesiologist), air (surgeon, anesthesiologist) or material (gloves, hands) contamination during or after two clinical PIPAC procedures. - Recommendation: toxicological analysis are performed before starting a clinical PIPAC program to ensure adequacy of the protective measures that are put in place.
Ndaw et al., (2018)	CP (Pt)	Pt	Patients	- To investigate the exposure to platinum compounds of medical staffs during a HIPEC and PIPAC procedure.	***PIPAC conditions*** - Remote control ***Exposure assessment*** - Wipes impregnated with water (GhostWipe) - Inductively coupled plasma mass spectrometry (ICP-MS)	***Surface contamination*** - Substantial contamination was observed on the PIPAC injector, syringe holder. - Heavy contamination was found on the floor within two meter from the operation table, which have resulted from a leak after the trocar were removed. - The contamination on the surgeon's outer gloves was detected, due to the removal of trocars and the laparoscopic incisions closure. - No contamination was found on the surgeon's hands after his gloves were removed.

Ametsbichler et al., (2018)	CP (Pt)	Pt	Patients	- To evaluate the contamination levels in real clinical conditions to minimize the occupational exposure risk, and to control.	***PIPAC conditions*** - Abdominal pressure: 12 mmHg - Spraying flow rate: 30 ml/min - Remote control ***Exposure assessment*** - PTFE filter (diameter, 37mm; pore size, 2.0 mm) - Flow rate: 2.3 m^3/hr - Sampling time: 51±7 min - Distance: 25 to 50 cm - Height: 1.5 m - Inverse voltammetry - LOD (pt): 0.02 ng/sample (wipe), 6 pg/sample (air)	***Airborne contamination*** - As long as no accidental leakage occurs, inhalation of A.D. aerosols by O.R. personnel are unlikely. ***Surface contamination*** - The surface contaminations by platinum were detected on all surface type (floor, injector, trocar). - The head ends of the trocars and parts of the injector devices (especially the syringe holder) were heavily and frequently contaminated. - Platinum traces at the O.R. floor was comparatively low. - Careful cleaning and disposal of the used equipment is of utmost importance to avoid cross-contamination.

***Abbreviation*:** A.D., antineoplastic drug; O.R., operation room; LOD, limit of detection; DX, doxorubicin; Pt, platinum; CP, cisplatin; OX, Oxaliplatin; Temp., temperature; R.H., relative humidity.

5. Conclusion

This study evaluated the occupational exposure of healthcare workers to three antineoplastic drugs via airborne and surface contamination during the administration of aerosol chemotherapy with the precessional motion. Air measurement was conducted at the locations of healthcare workers during the procedure, and surface contamination was evaluated on the devices used for the PIPAC procedure and the healthcare workers' protective equipment.

We did not detect doxorubicin and platinum in the air, but paclitaxel was detected. In addition, precessional motion does not appear to affect contamination of the air. Our key finding is the possibility of exposure when using paclitaxel. Healthcare workers might be at risk of inhaling paclitaxel. This possibility could arise for various reasons, so further research is needed.

The surface contamination levels of devices (spraying nozzles, telescope) directly inserted into the abdominal cavity were evaluated, and we confirmed a decrease in concentration associated with cleaning. For gloves, our findings were similar to those of previous studies, but the possibility of exposure to antineoplastic agents in masks and shoes was newly identified. Thus, it is possible that healthcare workers might experience dermal exposure through handling of antineoplastic drugs.

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Appendix

Table A-1. The surface samples during PIPAC procedure using doxorubicin

Day no.	Sampling location	Concentration (ng/cm^2)
# 1	Device	< LOD
	Right table	< LOD
	Around table	< LOD
	Nozzle tube	< LOD
# 2	Monitor table	< LOD
	Nozzle tube	< LOD
	Entrance door	< LOD
	Surgery light	< LOD
# 3	Around table 1	< LOD
	Around table 2	< LOD
	Around table 3	< LOD
	Nozzle fixing device 1	< LOD
	Nozzle fixing device 2	< LOD
	Surgery light 1	< LOD
	Surgery light 2	< LOD
	Injection nozzle	< LOD
	Injection nozzle and connector	128.56 [a]
	Pressure nozzle 1	< LOD
	Pressure nozzle 2	< LOD
	Camera Light	< LOD
	Camera connector	< LOD
	CO_2 injector	< LOD
	Precessional motion device	< LOD
# 4	Door surface (swine No.1)	< LOD
	Light source connector (swine No.1)	< LOD
	CO_2 injector (swine No.1)	< LOD
	CO_2 injecting connector	< LOD
	Surgery light (swine No.1)	< LOD
	Upper surface of monitor table (swine No.1)	< LOD
	Door surface (swine No.2)	< LOD
	Light source connector (swine No.2)	< LOD
	CO_2 injector (swine No.2)	0.70 [b]
	A.D. connector (swine No.2)	< LOD
	Upper surface of monitor table (swine No.2)	< LOD
	Surgery light (swine No.2)	< LOD

Abbreviation: LOD, limit of detection; A.D., antineoplastic drug.
[a] The leakage on the connector between injection tube and syringe.
[b] Cross-contamination with handling by surgeon.

국문초록

고압복강항암화학요법 시술 시
세 가지 항암제에 대한 노출 평가

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연구배경: 복막암종증은 치료의 어려움으로 인해 예후가 불량하며, 환자들에 대한 삶의 질을 개선하기 위하여 최근 유럽에서 고압복강항암화학요법이라는 기술을 개발 중에 있다. 그러나 본 요법은 의료진이 항암제에 노출될 수 있는 위험성이 존재하므로 이에 관한 연구가 필요하다. 본 연구의 목적은 국내에서 세차운동을 적용한 고압복강항암화학요법을 개발하는 시술 과정상에서 항암제에 의료진이 노출될 수 있는 가능성을 평가하고자 하는 것에 있다.

연구방법: 수술실에서 진행된 고압복강항암화학요법 시술에는 paclitaxel, cisplatin, doxorubicin의 세 가지 항암제가 사용되었다. 본 시술은 대형 돼지에 적용 되었다. 공기 중 시료 채취는 시술을 진행하는 의료진의 위치를 고려하여 수술대 근처에서 포집 하였다. 복강 내에서 분사되는

항암제 에어로졸에 직접 노출된 장치들과 의료진이 착용하는 보호구에 대해서 표면 시료를 확보하였다. Paclitaxel과 doxorubicin은 고효율 액체크로마토그래피 질량분석기(HPLC-MS/MS)로 분석하였으며, cisplatin은 유도결합플라즈마 질량분석기(ICP-MS)를 활용하여 백금 성분을 검출하고자 하였다.

결과: 전체 101개의 표면 시료와 56개의 공기 중 시료에서 각각 81개 (80.2%), 9개 (16.1%)가 검출되었다. 본 요법에 사용되는 장치들의 표면 시료는 총 52개 중 45개가 검출되었으며, paclitaxel과 백금의 기하 평균은 각각 1.94 ng/cm^2, 2.14 ng/cm^{2}로 나타났다. Paclitaxel은 최소 0.39 ng/cm^2 에서 최대 76.75 ng/cm^2 로 검출되었고, 백금은 0.02 ng/cm^2 에서 235.09 ng/cm^{2}까지 확인할 수 있었다. Doxorubicin의 경우는 확보된 10개의 시료 중 3개가 검출되었으며, 검출한계 미만부터 최대 3.86 ng/cm^2 수준으로 나타났다. 의료진이 착용한 보호구에 대해 표면 시료를 확보한 45개 중에서 36개가 검출되었는데, doxorubicin에 대해 확보된 4개의 시료는 전체 불검출이었다. Paclitaxel과 백금은 집도의와 간호사에서 검출한계 미만부터 각각 최대 0.62 ng/cm^2, 0.23 ng/cm^{2}의 수준인 것으로 확인되었다. 백금(n=16)과 doxorubicin(n=28)의 공기 중 시료는 전체 불검출이었으나, paclitaxel은 12개의 시료 중 9개에서 검출이 되었다. 해당 기하 평균은 42.05 ng/m^3 이었으며, 검출한계 미만부터 최대 87.81 ng/m^{3}까지 검출되었다.

결론: 새로운 화학요법인 고압복강항암화학요법을 국내에 도입하는 단계에서 사용된 세 가지 항암제에 대하여 의료진의 직업적 노출을 평가하였다. 표면 시료의 80% 이상이 검출되었는데, 이것은 피부

노출을 최소화하기 위해 주의가 필요하다는 것을 보여준다. 또한, 항암제의 준비, 희석, 주입, 취급 및 폐기 과정에서 항암제가 누출되어 오염될 수 있다. 두 가지 항암제(doxorubicin, cisplatin)는 공기 중에서 확인되지 않았으므로 흡입 노출의 가능성이 낮다고 판단되지만, paclitaxel은 공기 중에서 검출된 것으로 보아 흡입 노출이 발생할 가능성이 존재한다. 세 가지 항암제에 대한 노출기준은 현재 설정되어 있지 않으므로 가능한 낮은 수준으로 유지 및 관리되어야 한다.

주요어: 고압복강항암화학요법, 항암요법, 항암제, 직업적 노출, 의료진

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